

CORRESPONDENCE

Re: Multiple Births and Risk of Epithelial Ovarian Cancer

Multiple births may influence ovarian cancer risk, since they may reflect higher levels of gonadotropins or multiple ovulations, which have been related to ovarian carcinogenesis (1-3). The issue, moreover, is of specific interest in consideration of the debate on the possible role of fertility drugs, which stimulate ovulation, in ovarian carcinogenesis (4,5). A pooled analysis of eight studies conducted in the United States, Canada, and Australia and published in the journal, however, found no material association between multiple births and ovarian cancer risk (6).

To provide further information on the issue, we have, therefore, considered data from a multicentric case-control study conducted from January 1992 through September 1999 in greater Milan and the provinces of Pordenone and Gorizia in northern Italy, the province of Latina in central Italy, and the urban area of Naples in southern Italy (7).

Briefly, case patients were 1031 women admitted to the major teaching and general hospitals of the study areas, with incident, histologically confirmed epithelial ovarian cancer. The age range was 18-79 years, and the median age 57 years. Control subjects were 2441 women (age range, 17-79 years; median age, 57 years) with no history of cancer who were admitted to hospitals in the same areas as case patients for acute, non-neoplastic, nongynecologic conditions (26% traumas, 28% nontraumatic orthopedic diseases, 15% surgical conditions, and 31% miscellaneous other diseases). The distributions of case patients and control women were similar in terms of age and area of residence.

Information on reproductive factors included number of births (singleton and multiple), abortions, and stillbirths and age at each birth. Odds ratios (ORs) for multiple births and the corresponding 95% confidence intervals (CIs) were computed by use of multiple logistic regression models. The regression equation model included terms for age in

Table 1. Distribution of 1031 case patients with epithelial ovarian cancer and 2441 control subjects, according to type of birth (singleton only or multiple) (Italy 1992-1999)

Type of birth	No. of case patients	No. of control subjects	Odds ratio for ovarian cancer* (95% confidence interval)
Nulliparous	184	381	1.14 (0.41 to 1.42)
Singleton only	830	1989	1†
At least one multiple	17	41	0.89 (0.48 to 1.64)

*Estimates from multiple logistic regression equation, including terms for age, center, education, menopausal status/age at menopause, family history of ovarian and breast cancers, and oral contraceptive use.

†Reference category.

5-year intervals, area of residence, years of education, parity, menopausal status/age at menopause, family history of breast and ovarian cancers, and oral contraceptive use.

A total of 17 (1.6%) case patients and 41 (1.7%) control subjects had ever had multiple births. Only two control women and one case patient had more than one multiple birth; only one control had triplets. Compared with parous women with only singleton births, the multivariate OR for ovarian cancer for women with multiple births was 0.89 (95% CI = 0.48 to 1.24; Table 1). No significant heterogeneity was evident across strata of parity (OR = 0.70; 95% CI = 0.26 to 1.86 for women with one or two births; OR = 1.20 and 95% CI = 0.53 to 2.63 for those with three births). Only one (1.2%) of 81 women with mucinous ovarian cancer reported multiple births.

Our findings confirm that multiple births do not appear to influence subsequent ovarian cancer risk (6), regardless of the number of births. Multiple births were comparably rare in our dataset. Apart from the baseline characteristics of the population, this indicates that ovulation-inducing drugs (4,5) were not common in Italy in the generations of women included in this study.

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RESPONSE

We thank Dr. La Vecchia and co-workers for replicating our analysis in their case-control dataset of Italian women. It is interesting to note that their findings are essentially the same as ours (1). While the point estimate of the relative risk (0.89) in the Italian study was not significantly different from the null, the direction of the association was the same as in seven of the eight studies in our pooled analysis. These independent, confirmatory data, therefore, provide further support for our inference that mothers of twins (and other multiple

births) are at reduced risk of ovarian cancer. The question remains as to why this should be so.

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